Complete Summary

GUIDELINE TITLE

Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma.

BIBLIOGRAPHIC SOURCE(S)

Sarcoma Disease Site Group. Bramwell VH, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jul [online update]. 19 p. (Practice guideline report; no. 11-1). [27 references]

GUIDELINE STATUS

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COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Locally advanced or metastatic soft tissue sarcoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To determine if there is an advantage, in terms of response rate or survival, in using doxorubicin-based combination chemotherapy compared with single-agent doxorubicin for palliative treatment of incurable locally advanced or metastatic soft tissue sarcoma
- To determine if the use of combination chemotherapy is associated with increased toxic effects compared with the use of single-agent doxorubicin in this setting

TARGET POPULATION

Adult patients with symptomatic, unresectable, locally advanced or metastatic soft tissue sarcoma who are candidates for palliative chemotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Single-agent doxorubicin chemotherapy
2. Doxorubicin-based combination therapy, including doxorubicin with vincristine, vindesine, streptozotocin, cyclophosphamide, ifosfamide, dacarbazine, mitomycin-C, and/or cisplatin

MAJOR OUTCOMES CONSIDERED

- Response rate
- Overall survival
- Toxicity
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1999 Guideline

MEDLINE (Ovid) (from 1966) and CANCERLIT (Ovid) (from 1975) were searched in December 1997. "Doxorubicin" (Medical Subject Heading [MESH] term and text word) was combined with "Combin" (truncated text word), and these terms were then combined with search terms for the following study designs: practice guidelines, systematic reviews or meta-analysis, and randomized controlled trials. This search was updated in April and December of 1998, and again in June of 1999. EMBASE was also searched from 1979 to 1995 using the truncated keywords, "random" and "sarcoma". Citation lists and personal files were scanned for additional studies. The Physician Data Query (PDQ) clinical trials database (U.S. National Cancer Institute), the American Society of Clinical Oncology (ASCO) Annual Meeting Proceedings (1995-1999), and the Cochrane Library (Issue 2, 1999) were also searched for additional reports of completed or ongoing trials. No further attempt was made to find reports of unpublished randomized controlled trials. Relevant articles and abstracts were selected and assessed by two reviewers and the reference lists from these sources were searched for additional trials.

2004 Update

The original literature search has been updated using MEDLINE (through July 2004), EMBASE (1980 through July 2004), CANCERLIT (through October 2002), the Cochrane Library (Issue 3, 2004), and the 2000–2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials comparing single-agent doxorubicin with a doxorubicin-based combination chemotherapy regimen
2. Involved adult patients with locally advanced or metastatic soft tissue sarcoma in the palliative setting
3. Potential studies had to measure response rate, overall survival, and toxic effects or quality of life.
4. Abstracts of trials were also considered.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials.
2. Letters and editorials were not considered.
3. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

8 randomized controlled trials were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The intent was to combine (i.e., pool) data from all eligible trials, in order to calculate overall estimates of treatment efficacy and harm. Pooled results were expressed as an odds ratio (OR), which is the odds of an event occurring in the experimental group over the odds of an event occurring in the control group, with a 95% confidence interval (CI). Target events were consistently unfavourable (e.g., death at two years, no complete or partial response), so that estimates greater than 1.0 favoured the control group (single-agent therapy) and estimates less than 1.0 favoured experimental group (combination therapy). The more conservative random effects model was used in the meta-analyses to allow for the differences in trial design and quality. A statistical Q-test was used to measure the quantitative heterogeneity among study results. Calculations for the meta-analysis were performed on a Pentium PC using the software program, Metaanalyst[0.988], created by Dr. Joseph Lau (Boston, MA).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Members of the Sarcoma Disease Site Group (DSG) focused their discussion on the evidence for doxorubicin-based combination chemotherapy in advanced soft tissue sarcoma. It was discussed whether to include the doxorubicin, dacarbazine (DTIC), and ifosfamide (MAID) regimen in this guideline report, but since this regimen has not been tested in a randomized controlled trial comparing it with single-agent doxorubicin, it was excluded. It is given brief mention in the original guideline document.

There was some discussion on the quality and consistency of the trials included in this report. While all the studies included were randomized controlled trials, there was some variation as to the treatment regimens and dosages used, and the type and stage of tumour being treated. The studies also varied in the number of patients randomized, and the quality and level of detail reported in their methods and results. The DSG felt these differences should be noted in the guideline. The

group decided to add a sensitivity analysis to the meta-analysis, by combining data from the four studies using active agents in combination with doxorubicin (i.e., ifosfamide [IFOS] and dacarbazine [DTIC]) in order to see if this affected the results for response and survival outcomes.

While the group felt that more could be written on the increased adverse effects of combination chemotherapy as compared to single-agent regimens, they also recognized the difficulties in pooling adverse effects data that has been measured using different toxicity scales. The group decided not to combine adverse effects (toxicity) data, as this would be inappropriate.

There was also some discussion surrounding the lack of quality of life data and the use of response as an endpoint. Sarcoma studies are performed slowly, and many of the trials included in the report were completed before quality of life assessment tools were developed. Thus, response rate has been accepted as a surrogate for quality of life in patients in whom a response may relieve symptoms. The members of the DSG were in agreement that quality of life is an important end point and decided to add a point to the recommendation itself, stating that quality of life measures should be included as primary end points in future randomized clinical trials.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 53 practitioners in Ontario (29 medical oncologists, 11 radiation oncologists, eight surgeons, four gynecologists, and one pharmacist). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Sarcoma Disease Site Group.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Single-agent doxorubicin is an appropriate first-line chemotherapy option for advanced or metastatic soft tissue sarcoma. Some doxorubicin-based combination chemotherapy regimens, given in conventional doses, produce only marginal increases in response rates, at the expense of increased toxic effects, and with no improvements in overall survival.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of single-agent doxorubicin and doxorubicin-based combination chemotherapy for palliative treatment of incurable locally advanced or metastatic soft tissue carcinoma

POTENTIAL HARMS

Reporting of adverse effects was quite variable among the eight eligible trials. Most of the studies reported nausea/vomiting and hematological toxic effects. As all these studies were performed before the widespread use of $5HT_3$-antagonists, nausea and vomiting were reported frequently. Table 3 in the original guideline document shows that, with the exception of one study, nausea and vomiting were always greater for combination regimens, often significantly so. Similarly, hematologic toxic effects were reported in different ways among studies. Sometimes leucopenia and thrombocytopenia were reported separately, sometimes in combination. In many of these studies, nadir blood counts were not necessarily performed and there may be under-reporting of hematological toxicity. Again, Table 3 shows that the hematologic toxicity of combination chemotherapy was always higher than single-agent doxorubicin. Neutropenic fever was not reported consistently; neither were other toxic effects, such as mucositis. Although the more recent studies did report toxic deaths, these were uncommon across all the studies. Reporting of cardiotoxicity was highly variable and it was impossible to determine whether this was worse for single-agent or combination regimens; ultimately, it depended on the individual dose of doxorubicin received by each patient. Quality of life was not addressed in any of the studies included in this report.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation nor warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Nov 30 (updated 2004 Jul)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Sarcoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Sarcoma Disease Site Group disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Summary. Toronto

(ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2002. The information was verified by the guideline developer as of July 8, 2002. This summary was updated by ECRI on June 23, 2003. The updated information was verified by the guideline developer on July 16, 2003. This summary was most recently updated on October 6, 2004. The updated information was verified by the guideline developer on October 20, 2004.

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